September 20, 2001

Janice M. O'Polka
Project Manager
Industrial Health Foundation
34 Penn Circle West
Pittsburgh, PA 15206-3612

Dear Ms. O'Polka:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Cyclic Anhydrides, posted on the ChemRTK Web Site on April 17, 2001. I commend the Industrial Health Foundation Cyclic Anhydrides Committee for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

The category approach seems reasonable from the standpoint of structure and physicochemical properties. However, for health endpoints, EPA believes the Committee has not convincingly established that the members of this group in general have similar toxicologic properties. Nonetheless, the results of proposed testing of NMA have the potential to confirm the basis of the category for health endpoints. For aquatic toxicity, the category approach may be reasonable but the Committee needs to provide a rationale for expecting toxicological similarity. Furthermore, many inadequacies in the data and the study summaries compound the problem of evaluating the category for these endpoints.

EPA agrees with the proposed Test Plan for the SIDS health endpoints but would like the Committee to confirm EPA's understanding (see comments on Test Plan) of the plan for repeated-dose, reproductive and developmental toxicity testing. A suggested alternative approach for this endpoint appears in our comments. The Committee also needs to provide robust summaries for existing phthalic anhydride health data relied on in the Test Plan. Finally, two deficient genetic toxicity robust summaries need to be enhanced.

For fish and daphnia most of the summarized studies appear inadequate. Information missing from the remaining robust summaries needs to be supplied so that adequacy of the data can be determined.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that the Committee advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission: Cyclic Anhydrides

SUMMARY OF EPA COMMENTS

The sponsor, the Industrial Health Foundation Cyclic Anhydrides Committee, submitted a Test Plan and Robust Summaries to EPA dated March, 2001, for the Cyclic Anhydrides Category. EPA posted the submission on the ChemRTK HPV Challenge Web site on April 17, 2001. The proposed information-gathering plan is for five substances and mixtures (see Category Definition, below) considered by the sponsor to constitute a category.

EPA has reviewed this submission and has reached the following conclusions:

1. The category approach seems reasonable from the structure and physicochemical perspectives. For health effects it is also based in part on respiratory sensitization (see Category Justification). While the submitter has not convincingly established that the members of this group have similar toxicologic properties, the results of the proposed testing of NMA have the potential to confirm the basis of the category for health endpoints. The category approach for aquatic toxicity may be reasonable but the submitter needs to provide a rationale for expecting toxicological similarity (see Category Justification). Furthermore, many inadequacies in the ecotoxicity data and the study summaries compound the problem of evaluating the category for aquatic toxicity.

2. Physicochemical and Environmental Fate Data. EPA emphasizes that the submitter should provide measured data to fill most data gaps. For estimating the transport and distribution of these chemicals EPA recommends using the EQC Level III model; see specific comments under Test Plan.

3. Health Endpoints: EPA agrees with the proposed Test Plan for the SIDS health endpoints but would like the submitter to confirm EPA's understanding of the plan for repeated-dose, reproductive and developmental toxicity testing. A suggested alternative approach for this endpoint appears in the Test Plan section. In addition, the submitter needs to provide robust summaries and rationale for existing data relied on in the Test Plan (repeated-dose toxicity and reproductive toxicity studies with phthalic anhydride - an analog that is not a category member). Finally, there are two deficient robust summaries which, for the purposes of the U.S. HPV Challenge Program, need to be enhanced (genetic toxicity studies with THPA and HHPA - see specific comments below).

4. Ecological effects. It appears that for fish and daphnia most of the summarized studies are inadequate. The submitter needs to supply information missing from the remaining robust summaries so that adequacy of the data can be determined.

EPA requests that the Submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE CYCLIC ANHYDRIDE CHALLENGE SUBMISSION

Category Definition

The proposed category members are clearly identified as five substances and mixtures considered by the submitter to constitute a category: Hexahydrophthalic anhydride (HHPA, CAS No. 85-42-7), Methylhexahydrophthalic anhydride (MHHPA, CAS Nos. 25550-51-0 and 57110-29-9), Tetrahydrophthalic anhydride (THPA, CAS No. 85-43-8), Methyltetrahydrophthalic anhydride (MTHPA, CAS Nos. 34090-76-1 and 11070-44-3), and Nadic methyl anhydride (NMA; Methyl-5-norbornene-2,3-dicarboxylic anhydride, CAS No. 25134-21-8). Four of the five substances are very closely related structurally, while NMA differs somewhat in that it is a tricyclic rather than a bicyclic anhydride.

Category Justification

The submitter justifies this category by the structural similarity of the substances, their physical and chemical properties, and their toxicological properties. The chemicals in this category are structurally very similar, with the exception of NMA. NMA's tricyclic structure is more rigid than the bicyclic category members, which may affect some of its properties; however, examination of the properties presented in the Test Plan did not reveal significant differences across the category.

EPA agrees that the available information supports the part of the justification based on structural similarities and physical and chemical properties.

Toxicological similarities discussed by the submitter for health endpoints were limited to allergic sensitization, and although this similarity helps support the justification for the category, allergic sensitization is a very specialized toxicologic endpoint that cannot be used to infer toxicologic similarities for other endpoints. The submitter also refers to the fact that EPA's New Chemicals Program has identified cyclic carboxylic acid anhydrides as a category for pulmonary sensitization and a concern for reproductive or developmental toxicity (see www.epa.gov/opptintr/newchems/chemcat.htm).

EPA believes the submitter has not convincingly established that the members of this group in general have similar toxicologic properties. However, the results of proposed testing of NMA (see below) can be compared with the MTHPA data to see if other endpoints show a pattern or association that could strengthen the category for health endpoints.

For ecotoxicity the submitter needs to explain how the cyclic anhydrides' toxicity to aquatic organisms holds together for the entire category. The submitter should consider generally accepted approaches such as structure-activity relationships based on octanol/water partition coefficient (log P) using various models to compare predicted aquatic toxicity with experimental values.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

EPA agrees with the submitter's approach for melting point, boiling point, log P, and water solubility. EPA recommends that the submitter also provide measured data for vapor pressure. Generally, the log P value can be calculated for chemical classes that have been validated for the calculation. It is important that all endpoints other than log P be measured experimentally, as accurate information on physicochemical properties will help evaluate other data.

Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity)

EPA agrees with the submitter's proposal to complete environmental fate information for HHPA, MHHPA, THPA, and NMA by testing or modeling. However, the Test Plan summary matrix shows existing biodegradation data for MTHPA, whereas the robust summary states "no data"; this should be corrected.

Stability in Water. Given the lack of quantitative information this endpoint should be measured. Quantitative hydrolysis data will be important in evaluating the ecotoxicity data for these chemicals

Transport and Distribution. For estimating transport and distribution (fugacity), EPA recommends using the EQC Level III model, which is more realistic and useful than the Level I model for estimating a chemical's fate in the environment. In order to develop the Level III Fugacity model, EPA recommends using the EQC Level III Model from the Canadian Environment Modeling Center at Trent University, which allows full control of data inputs. This model can be found at the following web address: http://www.trentu.ca/academic/aminss/envmodel.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Acute Toxicity: EPA agrees that no further acute toxicity tests need to be performed.

Repeat Dose Toxicity: EPA agrees with the submitter's proposal to conduct a 90-day repeated-dose study with NMA and use the existing data for MTHPA (robust summary provided) and phthalic anhydride (surrogate aromatic compound that is not a category member and for which the existing data are not referenced or summarized). As a minimum, the submitter needs to supply the phthalic anhydride data (see specific comments below) and the rationale for its use.

Genetic Toxicity Data: EPA agrees with the proposed test plan for this endpoint. However, the THPA and HHPA robust summaries are deficient, and reference to phthalic anhydride data in the Test Plan narrative (page 13) needs to be supported with a reference and a robust summary (see specific comments below).

Reproductive and Developmental Toxicity: EPA agrees in principle with the proposed test plan, but has some concerns outlined below.

(1) EPA's understanding is that the submitter, anticipating from the acute data that NMA is more toxic than others in the group, plans to conduct a single test for this chemical that combines a one-generation reproduction study (OECD Guideline 415) and a 90-day oral toxicity study (OECD Guideline 408). EPA would like the submitter to confirm whether this interpretation of the planned testing is correct. An alternative approach to the one proposed is to perform a combined repeated dose toxicity and reproductive and developmental toxicity screening test (OECD Guideline 422), as was done with MTHPA, which would provide substantially equivalent data.

(2) The submitter notes that reproductive effects are a special concern because possible reproductive effects have been associated with the aromatic analog phthalic anhydride, but did not supply a related reference or robust summary.

Ecotoxicity

The robust summaries for all ecological end points were either inadequate or deficient (see Robust Summary comments, following section). For those endpoints that are deficient the submitter needs to supply missing data so that EPA can evaluate the adequacy of the test plan to satisfy the hazard screening needs of this proposed category.

The submitter plans to test NMA in fish (OECD Guideline 203), daphnid (OECD Guideline 202), and algae (OECD Guideline 201) to help characterize the cyclic anhydride category for ecotoxicity. EPA suggests using a closed system and mean measured concentrations while conducting these tests. EPA agrees with the proposed testing of NMA, but considers the existing data on other category members for fish and daphnid inadequate for the purpose of the Challenge Program (see specific comments below).

SPECIFIC COMMENTS ON ROBUST SUMMARIES

Physicochemical Properties

Most of the data provided by the submitter for these endpoints are referenced to Material Safety Data Sheets (MSDSs). The submitter needs to provide the underlying literature citations for MSDS values.

Biodegradation

EPA agrees with the submitter that lack of biodegradation may be due to a decrease in pH, possibly lethal to the microorganisms, brought about by the hydrolysis of the parent compound to the diacid. While technically the test data submitted are valid, more meaningful data could probably be derived with more attention to experimental design, such as control of pH during the test. However, this is outside the scope

of the Challenge program, and for screening purposes the submitted data can be regarded as adequate.

Health

Repeat Dose Toxicity. The submitter needs to provide the citation and a robust summary for the phthalic anhydride data to be used to support the proposed category.

Genetic Toxicity. The THPA and HHPA robust summaries are deficient, and reference to phthalic anhydride data in the Test Plan narrative (page 13) needs to be supported with a citation and a robust summary. The deficiencies in the THPA and HHPA Ames test summaries are: (a) no discussion of the use of appropriate positive controls; (b) no discussion of cytotoxicity relative to concentrations used; and (c) no elaboration on the concentrations used beyond reporting the maximum concentration.

Ecotoxicity Studies

Acute Aquatic Toxicity.

Robust summaries were submitted for studies on fish, daphnia, and green algae. Three 48-hour fish studies (MHHPA, HHPA, and THPA) were considered inadequate because these tests were not run long enough per OECD test guidelines and will likely give less than the optimum toxicity value for each endpoint tested. Likewise, two daphnid tests of only 24 hours' duration (THPA and HHPA) were considered inadequate for the same reason.

The MTHPA fish study is considered inadequate if a true 96-hour LC50 value was not determined; see comments below.

Critical experimental details or values were omitted from most of the remaining robust summaries. Please see EPA's guidance on how to enhance the robust summaries to the standard established in EPA's HPV Challenge Program Guidance at http://www.epa.gov/opptirtr/chemrtk/guidocs.htm.

HHPA and THPA

Algae. Some essential experimental details missing from the study summary include: pH, hardness, TOC, DO, temperature, test substance purity, and vessel type.

MTHPA

Fish. The critical data element missing is a true 96-hour LC50 value; the value reported was ">100 mg/L", but only when a fish LC50 value is >1000 mg/L is there no need to provide an exact LC50 value. In addition, hardness, vessel type, TOC, pH, test substance purity, temperature, and DO were some of the required data not provided.

Algae. Some missing experimental details from the summary included: pH, hardness, TOC, DO, temperature, test substance purity, and vessel type.

Daphnia. The information provided was too sparse for an evaluation of data adequacy. Some missing experimental details from the 48-hour exposure in the daphnid test are pH, hardness, temperature, test substance purity, and DO.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.